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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/803,687	03/09/2001	David T. Scadden	0492479-0018	7008

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EXAMINER	
KATCHEVES, KONSTANTINA T	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/803,687	SCADDEN ET AL.	
	Examiner	Art Unit	
	Konstantina Katcheves	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45 and 75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-45 and 75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-45 and 75 are pending in the present application.

Response to Amendment

The rejection of claims 1, 2, 30-32 and 36-42 and 45 under 35 U.S.C. 102(b) as being anticipated by Waldman et al. (Cancer Research Vol. 55 1995) has been withdrawn in view of Applicant's amendment filed 10 October 2003.

The rejection of claims 1, 2, 3, 30-32 and 36-42 and 45 under 35 U.S.C. 102(b) as being anticpated by Nakanishi et al. (PNAS Vol.92 1995) has been withdrawn in view of Applicant's amendment filed 10 October 2003.

The rejection of claims 1-21, 27 and 30-45 under 35 U.S.C. 103(a) as being unpatentable over Nakanishi et al. as applied to claims 1, 2, 3, 30-32 and 36-42 and 45, and further in view of Rivard et al. (Journal of Biological Chemistry vol.271 1996) has been withdrawn in view of Applicant's amendment filed 10 October 2003.

The rejection of claims 3-6 and 22-29 under 35 U.S.C. 112, first paragraph, failing to meet the written description requirement has been withdrawn in view of Applicant's arguments filed 10 October 2003

The rejection of claims 1-45 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of Applicant's arguments filed 10 October 2003.

New Grounds of Rejection Necessitated by Applicant's Amendment

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 4, 6-11, 13, 15-18, 20, 22-29, 30, 33, 36-41, 43-45 and 75 are rejected under 35 U.S.C. 102(b) as being anticipated by Roberts et al. (US Patent No. 5,958,769).

The invention of the present claims is drawn to a method of expanding a population of stem or progenitor cells by providing such a cell with less than wild-type p21 and/or p27 activity. Moreover, the claims are drawn to these cells by administration of an inhibiting agent which includes antisense agents.

Roberts et al. disclose a method for increasing the proliferation of various cells by administering inhibitors of p27 cyclin dependent kinase. See abstract and column 2, lines 59-62. The cell populations include stem cells, progenitor cells, fibroblasts, myeloblasts, neurons, epithelial cells, hematopoietic progenitor cells, granulopoietic and embryogenic cells. See column 2, lines 64 to column 3 lines 11, column 20, and example 5. Roberts et al. disclose that the p27 inhibitor may be used with antagonists of p21 to increase the proportion of proliferating cells in a population. The agents include any compound, protein or antisense agent that inhibits p21 and/or p27. See column 8, lines 8-38.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-45 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roberts et al. as applied to claims 1, 3, 4, 6-11, 13, 15-18, 20, 22-29, 30, 33, 36-41, 43-45 and 75 above, and further in view of Waldman et al. (Cancer Research Vol. 55 1995, cited in prior action).

The invention of the present claims is relied upon as described above further comprising erythropoietic, thrombogenic, fetal and mesenchymal cells. Moreover, the invention further comprises an embodiment wherein the cells have discrupted p21 and/or p27 genes.

Roberts et al. is relied upon as described above. However, Roberts et al. fail to specifically teach erythropoietic, thrombogenic, fetal and mesenchymal cells and also fail to teach disruption of p21 and/or p27 genes.

Waldman et al. teach a method wherein clones comprising a homozygous deletion of p21 resulted in the abrogation of the G_1 cell cycle checkpoint such that all cells passed through S phase and resulted in the growth and proliferation of the cells. See abstract and page 5189
It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Roberts et al. and Waldman et al. to proliferate cells by disrupting both p21 and p27 in a cell population. One of ordinary skill in the art would have been motivated to combine the above references because the references teach p21 and p27 inhibit Cdk

activity in a cell and since both references teach that inhibition of each gene results in cell proliferation and abrogation of cell quiescence, one of skill in the art would reasonably expect to promote cell proliferation by inhibiting both p21 and p27. Moreover, techniques of cell culture and proliferation are germane in the art such that the ordinary skilled artisan would be motivated to proliferate many different cell types including stem and progenitor cells. Additionally, the disclosure of Roberts et al. is not limited to the cell types disclosed. Because Roberts et al. discloses a very broad range of cells and the common techniques of cell culture and proliferation, it would have been obvious to one of skill in the art to use the present invention with these and other cell types disclosed. Thus, the invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27 and 75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for other inhibiting agents, does not reasonably provide enablement for antisense agents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re*

Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

The nature of the invention and the breadth of the claims.

Methods of targeting nucleic acids to specific genes in order to inhibit or alter expression fall into the area of antisense. The present claims are broadly drawn to a method of delivering and exogenous antisense nucleic acid to a cell to inhibit activity of p21 and/or p27.

The state of the art, skill of those in the art and predictability of the art.

The state of the art today is not predictable for antisense. Branch states that while scientists and pharmaceutical developers are working to find nucleic-acid based therapies, the unpredictability of the art has confounded research applications. See Branch TIBS 23:45-50 1998 see page 45 and page 46. Such impediments include barriers created by the internal structures of target RNAs and their associations with cellular proteins. See page 45 and the section entitled "The three As of ..." on pages 48-49. Additionally, target site specificity is an

issue, and Branch states that it remains to be determined whether there are recognition sequence lengths will allow a unique RNA to be selectively destroyed. See page 48, center column.

The amount of guidance provide and the presence of working examples.

The quantity of experimentation required to practice the invention as claimed would require the *de novo* identification of antisense oligonucleotides which would bind accessible regions of target sequences and would require the de novo identification of antisense oligonucleotides that have functionality *in vivo* and that are also specific. As discussed above, the disclosure and examples in the specification are limited. No specific guidance is instantly taught in the specification.

Based on the complex nature of the invention, the state of the prior art, the unpredictability of the art, the lack of sufficient guidance or working examples in the specification for antisense methods, and the breadth of the claims, an undue amount of experimentation would be required for one of skill in the art to practice the claimed invention.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Konstantina Katcheves whose telephone number is (571) 272-0768. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday 7:30 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Konstantina Katcheves
Group Art Unit: 1636
1 April 2004

JAMES KETTER
PRIMARY EXAMINER